Zerolatum Plus

PL 18962/0008

UKPAR

TABLE OF CONTENTS

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PL 18962/0008

LAY SUMMARY

The MHRA granted Zeroderma Ltd a Marketing Authorisation (licence) for the medicinal product Zerolatum Plus (product licence number: 18962/0008) on 24 May 2007. This medicine can be bought from pharmacies and other outlets without prescription.

Zerolatum Plus is a softening, moisturising and protective formulation for topical use in the treatment of eczemas at risk of infection. This product contains the active ingredients light liquid paraffin, benzalkonium chloride and irgasan PG 60 (triclosan).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Zerolatum Plus outweigh the risks; hence a Marketing Authorisation has been granted.

Zerolatum Plus

PL 18962/0008

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The application for Zerolatum Plus (PL 18962/0008) was submitted as a standard abridged application, according to Article 10a of Directive 2001/83/EC, cross referring to Oilatum Plus (PL 00174/0070), which was licenced to Stiefel Laboratories (UK) Ltd in the UK on 16 February 1990.

The product is intended for use as a bath emollient for topical use in the prophylactic treatment of eczemas at risk of infection. Zerolatum Plus contains three active ingredients: light liquid paraffin, an emollient and benzalkonium chloride and irgasan PG 60 (triclosan), antibacterial agents with efficacy against staphylococcus aureus, the principal causative organism in infected eczemas

As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for it.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Light liquid paraffin

An appropriate specification based on the European Pharmacopoeia has been provided.

Batch analysis data are provided and comply with the proposed specification.

The manufacturer of the finished product retests this active substance before use to ensure that it complies with the Ph Eur monograph.

No stability studies were considered to be necessary on light liquid paraffin.

Benzalkonium chloride solution 50% w/v

An appropriate specification based on the European Pharmacopoeia has been provided.

Batch analysis data are provided and comply with the proposed specification.

The manufacturer of the finished product retests this active substance before use to ensure that it complies with the Ph Eur monograph.

Appropriate stability data have been provided for this active substance.

Irgasan PG 60 (Triclosan)

An appropriate specification based on the European Pharmacopoeia has been provided.

Batch analysis data are provided and comply with the proposed specification.

The manufacturer of the finished product retests this active substance before use.

Appropriate stability data have been provided for this active substance.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely crodalan AWS, isppropyl palmitate, oleyl alcohol and macrogol lauryl ether (Laureth-4). Appropriate justification for the inclusion of each excipient has been provided.

The excipients, isopropyl palmitate, oleyl alcohol and macrogol lauryl ether complied with their Ph Eur monographs. Crodalan complied with in-house specifications. Satisfactory certificates of analysis have been provided for all excipients.

The formulation contains the same active ingredients, in the same proportions, as Oilatum Plus (PL 00174/0070) which has been available on the UK market for over 10 years, although, there are some differences in the excipients.

None of the active ingredients or excipients used in the formulation are of animal origin and all comply with the EC guidelines relating to TSE. A statement to this effect is provided.

Manufacture
Zerolatum Plus solution is manufactured according to good manufacturing practice using equipment and manufacturing facilities which are suitable for the manufacture of topical liquids.

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. The validation data obtained show that the proposed method of manufacture gave a product which was reproducible and of good quality.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is to be marketed in standard pharmaceutical packaging materials comprising of white high density polyethylene bottles with polypropylene screw cap The manufacturer's specifications and control tests for the bottle and cap are given and are satisfactory.

No studies have been carried out on the packaging, other than the stability studies on the finished packed product which are considered to be satisfactory for the presentation.

Stability of the finished product
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 12 months for the unopened product and 6 months after first opening the container with the storage instruction 'Do not store above 25°C' is acceptable.

Product literature
All product literature is satisfactory.

CONCLUSION

Zerolatum Plus is a simple emollient product intended for topical administration. The formulation is based on that of a currently approved product, Oilatum Plus, and uses well established ingredients and pharmaceutical excipients.

In conclusion, a product licence may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data has been supplied with these applications and none is required for applications of this type.

CLINICAL ASSESSMENT

INDICATIONS
For the prophylactic treatment of eczemas at risk from infection.

DOSE & DOSE SCHEDULE
Topical as a bath additive.
Zerolatum Plus should always be diluted with water. It is an effective cleanser and should not be used with soap.
Adults and children: In an eight inch bath add 2 capfuls, in a four inch bath add 1 capful.
Infants: Add 1ml (just sufficient to cover the bottom of the cap) and mix well with water.
Do not use for babies younger than six months.

TOXICOLOGY
The formulation of Zerolatum Plus is based on that of a currently approved product, Oilatum Plus, and uses well established pharmaceutical ingredients and excipients which have a long history as safe and effective agents for application to the skin. The components of the product have all been demonstated to be absorbed through human skin to a very limited degree and no systemic toxicity would be expected to arise from the recommended external usage of the preparation. The Applicant has included an extensive bibiographical review and the toxological profiles of the antimicrobial substances benzalkonium chloride and triclosan have been reviewed in detail. No preclinical studies have been performed with Zerolatum Plus and such studies are considered unnecessary and are difficult to justify because the low levels of the antimicrobial substances present and because of the extensive toxicological data available on both of them. Zeroneum Plus is likely to be a safe product when used according to the directions and precautions detailed in the SPC.

CLINICAL PHARMACOLOGY

Pharmacodynamics
ATC-CODE: DO2A

Benzalkonium chloride and triclosan are anti-bacterial agents with proven efficacy against *staphylococcus aureus*, the principal causative organism in infected eczemas. Light liquid paraffin is an emollient widely used in the treatment of eczema.

Pharmacokinetics
Pharmacokinetics are not applicable to a topical formulation with direct emollient action upon the skin.

Bioequivalence
Not applicable.

EFFICACY
Zerolatum Plus can be considered similar to the currently approved cleansing, emollient and antibacterial product Oilatum Plus. The Applicant requests equivalent therapeutic indications to these products in their proposed SPC. A review of the literature supports the use of this product.

SAFETY
No new data are submitted and none is required for this type of application.

EXPERT REPORT
A medically qualified consultant in pharmaceutical medicine has provided a satisfactory expert report.

A consultant in pharmacology and toxicology has submitted a satisfactory pharmaco-toxicological expert report.

PRODUCT LITERATURE
No Patient Information leaflet has been submitted with this Application. This is acceptable as all of the necessary patient information is included on the labelling. All other literature is satisfactory.

DISCUSSION
Zerolatum Plus, containing light liquid paraffin (52.5% w/w), benzalkonium chloride solution (12.0% w/w) and triclosan (2% w/w) contains the same active ingredients, in the same proportions, as the currently licensed product Oilatum Plus. There are some differences in the excipients, however, these are well characterised components which have been used pharmaceutically for many years. This bibliographical application has justified the therapeutic rationale for the product and has provided reassurrance regarding the safety and efficacy profile which is to be expected.

MEDICAL CONCLUSION
A Marketing Authorisation may be granted for this application.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Zerolatum Plus are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

The efficacy of the active ingredients has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been demonstrated for Zerolatum Plus in the therapeutic indications proposed. The risk benefit is therefore considered to be positive.

Zerolatum Plus

PL 18962/0008

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 21 May 2002
	Following standard checks and communication with the applicant the MHRA considered the application valid on 11 June 2002
3	Following assessment of the application the MHRA requested further information on the clinical dossier on 12 July 2002 and on the quality dossier on 23 July 2002. The applicant responded to the MHRA's requests, providing further information on 25 June 2003.
4	The MHRA requested further information on the quality dossier on 1 August 2006. The applicant responded to the MHRA's requests, providing further information on 17 August 2006.
5	The MHRA requested further information on the quality dossier on 9 October 2006. The applicant responded to the MHRA's requests, providing further information on 10 October 2006.
	The MHRA requested further information on the quality dossier on 8 November 2006. The applicant responded to the MHRA's requests, providing further information on 15 May 2007.
7	The applications were determined on 24 May 2007.

1 NAME OF THE MEDICINAL PRODUCT

Zerolatum Plus

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Light liquid paraffin 51.66% w/w.
Benzalkonium chloride solution (50%w/v) 12.0% w/w equivalent to Benzalkonium chloride 6% w/w.
Irgasan PG 60 3.34%w/w equivalent to Triclosan 2.0%w/w
For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Cutaneous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ATC Code: DO2A
For the prophylactic treatment of eczemas at risk from infection.

4.2 Posology and method of administration

Topical as a bath additive.
Zerolatum Plus should always be diluted with water. It is an effective cleanser and should not be used with soap.
Adults and children: In an eight inch bath add 2 capfuls, in a four inch bath add 1 capful.
Infants: Add 1ml (just sufficient to cover the bottom of the cap) and mix well with water.
Do not use for babies younger than six months.

4.3 Contraindications

Patients with a known hypersensitivity to any of the ingredients should not use the product.

4.4 Special warnings and precautions for use

Avoid contact of the undiluted product with the eyes. If the undiluted product comes into contact with the eye, reddening may occur. Eye irrigation should be performed for 15 minutes and then the eye examined under fluorescein stain. If there is persistent irritation or any uptake of fluorescein, the patient should be referred for ophthalmological opinion.
The product should not be used with soap.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

No restrictions on the use of the product in pregnancy and lactation are proposed.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

None known.

4.9 Overdose

The product is intended for topical use only. Accidental ingestion may cause gastrointestinal irritation with vomiting and diarrhoea. Vomiting may result in foam aspiration. In the case of accidental ingestion, give 1 to 2 glasses of milk or water to drink. If a large quantity of the product is ingested, the patient should be observed in hospital and the use of activated charcoal may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Benzalkonium chloride and triclosan are anti-bacterial agents with proven efficacy against *Staphylococcus aureus*, the principal causative organism in infected eczemas.
Light liquid paraffin is an emollient widely used in the treatment of eczema.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crodalan AWS (polysorbate 80, cetyl, stearyl and oleyl acetates and acetylated lanolin alcohol)
Isopropyl palmitate
Oleyl alcohol
Macrogol 4-lauryl ether (Laureth - 4)
Polypropylene glycol [ingredient of Irgasan PG60 (triclosan)]

6.2 Incompatibilities

None known.

6.3 Shelf life

12 months (unopened).

6 months after first opening container.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
White high density polyethylene bottles with polypropylene screw cap containing 500ml of liquid.

6.6 Special precautions for disposal
There are no special instructions for use or handling of Zerolatum Plus.

7 MARKETING AUTHORISATION HOLDER

Zeroderma Ltd
Manor House
Victors Barns
Brixworth
Northampton NN6 9DQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 18962/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/05/2007

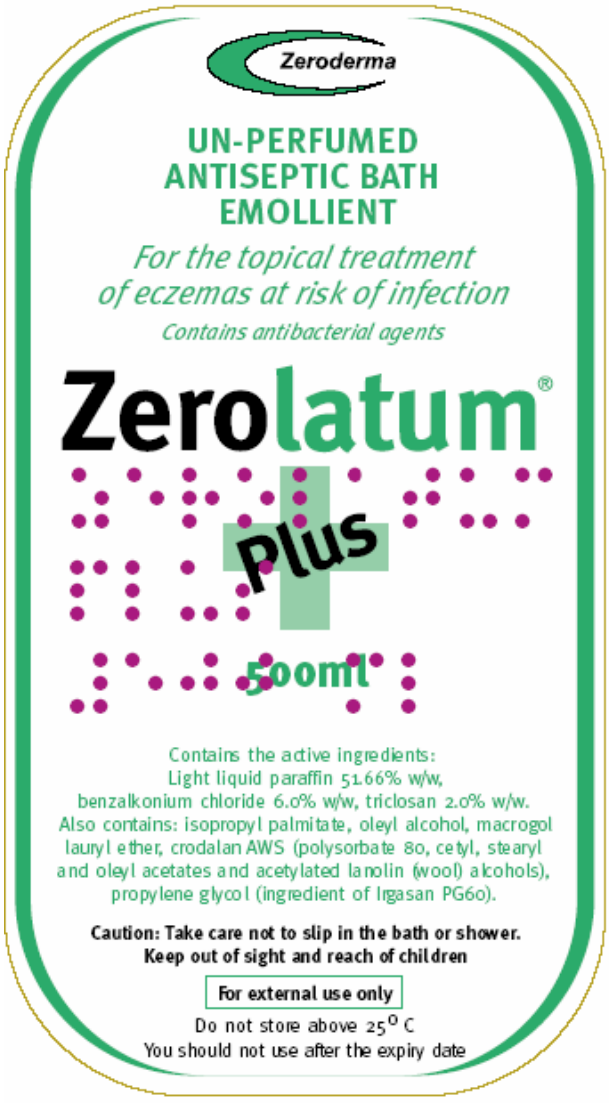
10 DATE OF REVISION OF THE TEXT

24/05/2007

PATIENT INFORMATION LEAFLET

No Patient Information Leaflet (PIL) has been submitted for this product, this is satisfactory as all necessary information is included on the product labels.

LABELLING


Zeroderma
UN-PERFUMED
ANTISEPTIC BATH
EMOLLIENT
For the topical treatment
of eczemas at risk of infection
Contains antibacterial agents
Zerolatum®
plus
500ml
Contains the active ingredients:
Light liquid paraffin 51.66% w/w,
benzalkonium chloride 6.0% w/w, triclosan 2.0% w/w.
Also contains: isopropyl palmitate, oleyl alcohol, macrogol
lauryl ether, crodalan AWS (polysorbate 80, cetyl, stearyl
and oleyl acetates and acetylated lanolin (wool) alcohols),
propylene glycol (ingredient of Irgasan PG60).
Caution: Take care not to slip in the bath or shower.
Keep out of sight and reach of children
For external use only
Do not store above 25° C
You should not use after the expiry date


Zerolatum®
Plus
500ml
Dosage and application:
You should not use Zerolatum Plus neat on your skin. It should always be diluted with water. Do not use soap.
Add 2 capfuls to an 8 inch bath
Infants – not suitable for babies under 6 months.
Add 1ml (cover the bottom of the cap) to bath and mix well with water. Soak for 10-15 minutes and gently pat skin dry. Use once daily. If symptons persist consult your doctor.
Warning:
If undiluted product is swallowed, drink 1-2 glasses of milk or water and seek medical advice.
Avoid contact with the eyes. If this should occur, rinse immediately with clean water.
Do not use this product if you are sensitive to any of the ingredients. If you find you are sensitive to the product, stop using it. If you experience any unwanted effect that is severe or lasts for more than a few days, tell your doctor. If you have any queries about this bath oil, or are not sure about anything, consult your pharmacist or doctor.
The Product Licence Holder is: Zeroderma Ltd, Victors Barns, Brixworth, England NN6 9DQ
PL Number: 18962/0008
Manufactured by: Ovelle Pharmaceuticals Coe's Road, Dundalk, IRELAND
Date of preparation: October 2004
BARCODE AREA